II. Prospects for Chemical Treatment of Emphysema

Introduction

GORDON L. SNIDER

Emphysema is defined as permanent enlargement of the respiratory air spaces of the lungs with destruction of their walls. All would agree that we do not know enough about the mechanisms of lung repair to have any hope of restoring emphysematous lung tissue to normal. But the development during the last two decades of the hypothesis that damage to the elastic fiber network of the lung underlies the development of emphysema, and that this damage is due to an imbalance of proteases and antiproteases in the lungs, clearly provides the opportunity for preventing emphysema. The evidence supporting this hypothesis is still fragmentary and largely indirect. The question obviously arises as to whether attempts to prevent emphysema by chemical treatment should be deferred until understanding of the basic pathogenetic mechanisms is more complete. There are many precedents for not doing so. Digitalis was used for treating heart failure and penicillin was successfully used for treating many infections long before the mechanisms of action of these drugs became clear. It seems entirely reasonable to attempt to manipulate the protease-antiprotease system in the lungs before we understand all its nuances.

Clinical trials requiring multi-center efforts are among the most expensive of all biologic research endeavors. In the first paper in this section, Hurd sets forth the consultative and administrative procedures for undertaking such research under the aegis of the Division of Lung Diseases (DLD) of the National Heart, Lung, and Blood Institute. Few other fund-granting agencies can afford to support such investigations.

The evidence supporting the protease-antiprotease hypothesis of emphysema is much more compelling in subjects with homozygous alpha-1-protease inhibitor deficiency than it is in genetically normal persons. However, this genetically determined form of emphysema comprises at most a few percent of the total population of individuals with emphysema. The problems of finding subjects with homozygous alpha-1-protease inhibitor deficiency before they have severe emphysema are formidable. Burrows, analyzing the results of the first two meetings of a DLD Working Group for Evaluation of Elastase Inhibitor Therapy in Pulmonary Emphysema, points out in the second paper the need for deciding when in the course of their disease such individuals should be studied. However, statistical projections indicate that 300 to 500 PiZ subjects with mild airways obstruction would need to be followed for a minimum of three years. Quite apart from the matter of expense, the enrollment of such a large number of PiZ subjects in a controlled trial of replacement therapy would be a difficult task, if indeed it is possible.

In the third paper of this section, Buist summarizes the results that were finally developed by the DLD workshops on the natural history of air-flow obstruction in groups of PiZ individuals collected in many institutions in the United States and in Sweden. As already noted, the chief purpose of these workshops was to determine the feasibility of a clinical trial of antiproteolytic therapy in PiZ individuals. Final analysis was limited to 105 subjects with a PiZ phenotype and with duration between first and last $FEV_{1.0}$ measurements of 12 or more months. Workshop participants fully recognized the limitations of retrospectively collected data. Furthermore, in some instances, affected persons presented as patients, and in other instances they were identified by screening of patients' relatives, blood bank samples, or persons participating in population studies. There is no assurance that the cases are representative of all PiZ subjects.

Within these limitations, the study provides information on changes over time of the $FEV_{1.0}$ in PiZ individuals that are now not available. It is not surprising that there was a high mortality but quite a low calculated mean rate of annual decline (45 ml/yr) in 52 PiZ subjects with $FEV_{1.0}$ values below 30% of predicted. Neither is it very surprising that 71 PiZ subjects with initial $FEV_{1.0}$ values between 30 and 65% of predicted had a mean rate of decline in $FEV_{1.0}$ of 107 ml/yr, a value almost twice the average rate of decline in patients (presumably non-PiZ) with ordinary COPD. The finding of 22 subjects with initial $FEV_{1.0}$ values greater than 65% of predicted who showed a relatively low mean rate of decline in $FEV_{1.0}$, 41 ml/yr, is of greater interest; these persons were mostly detected in population surveys. Thus, there is a population of PiZ individuals with moderate to severe air-flow obstruction who go through a period of relatively rapid functional decline, and these individuals would be suitable for entry into a clinical trial of the efficacy of antiprotease therapy. But those with very severe and those with very mild air-flow obstruction would not be suitable for such a trial. These data also suggest that advertising would be a more suitable way of finding PiZ subjects willing to volunteer for an antiprotease trial than population surveys of well people. The observations that some PiZ subjects with mild disease have a slow rate of functional deterioration is intriguing and seems worthy of further study.

In Glaser's paper, a method is described that should be readily adaptable to commercial-scale production for isolating alpha-1-protease inhibitor from Cohn Fraction-IV-1, a relatively unused side product in the worldwide production of albumin and immunoglobulin from human plasma. The method depends on the finding that alpha-1-protease inhibitor has a single, unusual disulfide bond that consists of a cysteine-containing region covalently linked to a free cysteine or glutathione via a disulfide bridge. The linkage can be broken by reductants without adversely affecting the stability or the protease-inhibitory activities of the protein. This finding permits the removal of contaminating proteins by salting out in the presence of strong reductants. Further purification of the product is carried out with DEAE-anion exchange chromatography. In order to minimize the high risk of contamination by hepatitis virus, a specifically developed pasteurization procedure is carried out.

Gadek and colleagues, using a different preparation of alpha-1-protease inhibitor, have demonstrated that blood and bronchoalveolar lavage levels of alpha-1-protease inhibitor can be raised to normal levels by weekly intravenous injections of the protein into persons with homozygous alpha-1-protease inhibitor deficiency. No side effects of treatment were encountered with 4 weekly treatments in 5 persons. Thus, the scene is set for the assumption by alpha-1-protease inhibitor of a major role in the preventive management of emphysema in alpha-1-protease inhibitor-deficient individuals. Needless to say, no private manufacturing company will undertake the commercial development of alpha-1-protease inhibitor without the assurance that a case-finding program and subsidization of treatment of alpha-1-protease inhibitor deficient individuals would follow.

Powers, in the final paper in this section, summarizes what is known of the chemical-

ly active site of human neutrophil elastase. He discusses a number of potent reversible and irreversible inhibitors that have been developed for this enzyme. Several of these agents have been shown to be effective in preventing elastase-induced emphysema in animal models of the disease. However, little is known of the toxicity or pharmacology of these inhibitors and much work still needs to be done with them.

It is plain that other than for efforts bent toward decreasing the smoking of tobacco, the preventive management of emphysema is still a concept that is difficult and far off. But it is important to recognize that the approaches set forth in this section were not even dreamed of two decades ago. They are all the fruits of medical research that have cost but a tiny fraction of the sums of money that have been spent to care for the victims of emphysema. It seems clear that serious impediments, logistic, scientific and economic, stand in the way of a major initiative for the preventive management of emphysema in the near future. It can hardly be argued that, while these difficult decisions are being dealt with, government, industry, and private research organizations would do well to continue supporting basic research efforts in the pathogenesis of emphysema.

GORDON L. SNIDER, *Editor*
Boston University, Boston

What Are the Prospects for Getting the Current Theories Adequate Clinical Trials?[1,2]

SUZANNE S. HURD

Introduction

In October 1978, the Division of Lung Diseases, National Heart, Lung, and Blood Institute, convened a group of experts to consider the advisability and feasibility of developing and testing agents for the treatment of human pulmonary emphysema. The group was asked to evaluate the possibility of treating: (*1*) patients with a genetic deficiency of alpha-1-antitrypsin with isolated human alpha-1-antitrypsin or synthetic low molecular weight elastase inhibitors, and (*2*) treating more common varieties of emphysema with the elastase inhibitors. Based on available data, the conferees agreed in principle that it might be possible to treat emphysema, but they identified several formidable problems that would have to be solved before clinical trials of these therapies could be undertaken (*1*).

A proposed plan to meet these goals was divided into three phases. *Phase 1*: (*1*) Determine the natural history of emphysema in patients with phenotype PiZZ for alpha-1-antitrypsin. (*2*) Develop methods for isolation of alpha-1-antitrypsin. (*3*) Set up a means of testing the safety of elastase inhibitors. (*4*) Encourage development of new elastase inhibitors. (*5*) Encourage the development of biochemical means of detecting lung destruction in patients with emphysema. *Phase 2*: (*1*) Design the study of therapy of patients with PiZZ phenotypes and identify and enroll patients. (*2*) Produce therapeutic amounts of alpha-1-antitrypsin, prove its safety in animals and people, and determine the clinical usefulness in patients. (*3*) For common emphysema, produce therapeutic amounts of elastase inhibitors, prove safety in animals and people, and determine the clinical usefulness in patients. At phase 3, clinical trials would be conducted.

Many steps have been taken to meet the goal of improved management of emphysema, as evidenced from other presentations in this symposium. Although clinical investigations to demonstrate feasibility of alpha-1-antitrypsin replacement therapy in PiZZ subjects have been reported (*2*), clinical trials to provide the definitive validation step in testing the efficacy of this treatment regimen before it is introduced into practice have not yet been initiated. What are the prospects for getting the current theories relating to the treatment of pulmonary emphysema adequate clinical trials?

The Clinical Trial

The National Heart, Lung, and Blood Institute supports a large number of basic, clinical, and applied research projects that have as their objective understanding the etiology and pathogenetic mechanisms involved in disease processes. However, translation of results from the basic and clinical scientist into specific application for diagnosis and treatment of disease is an important step that must be taken. The clinical trial represents a mechanism whereby therapeutic modalities, among others, can be tested and validated before introduction into the health care system. A clinical trial may also be undertaken in order to determine which of several alternative treatments already in use are most effective.

Clinical trials have been defined (*3*) as cohort studies in which treatment is initiated specifically for evaluation and not just during the care or observation of patients. Such trials are further classified into uncontrolled trials, in which there is no concurrent comparison group; nonrandom controlled trials, in which concurrent comparison groups are allocated by means of some nonrandom process; and randomized controlled trials, in which subjects are randomly allocated into treatment and control groups. Depending on the hypothesis to be tested and the endpoint of the study, a clinical trial may be undertaken in a single center with just a few subjects or it may require participation of several centers or clinics to engage in a collaborative effort involving many subjects.

The steps to initiate a clinical study require the concerted effort of basic scientists and clinicians who must be confident that the scientific and medical basis of the proposed study is valid. If new drugs are to be tested, clearance procedures with the Federal Food and Drug Administration must be initiated. If a large amount of specific biomaterials are required, procedures for large scale production must be available and a process initiated to prepare sufficient amounts for testing purposes. Financial resources must be available to assure long-term commitment to participants in a clinical study. At a time when there are more demands on fewer Federal funds for research, the decision to implement a clinical trial through the NIH has become more critical. These trials are often expensive to undertake because of the need to involve multiple clinical centers over a long period of time to enroll sufficient numbers of subjects and follow them until the therapy can be effectively evaluated.

Steps in Initiation of a Clinical Trial: The Research Grant

The National Heart, Lung, and Blood Institute has provided financial support for

[1] From the Division of Lung Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Department of Health and Human Services, Bethesda, Maryland.

[2] Requests for reprints should be addressed to Suzanne S. Hurd, Ph.D., Division of Lung Diseases, National Heart, Lung, and Blood Institute, National Institutes of Health, Westwood Bldg., Room 6A16, 5333 Westbard Ave., Bethesda, MD 20205.

many clinical studies through several different mechanisms. A single investigator or a group of investigators may choose to develop and design a clinical research investigation and submit a regular research grant. If adequate numbers of subjects are available to test the hypothesis and the necessary biostatistical skills are available, a single center trial is feasible. However, if multiple institutions are required in order to enroll adequate numbers of subjects or to minimize influence of geography, climate, or lifestyle, a group of investigators could decide to develop a common study protocol with biostatistical expertise included either in one of the cooperating clinical centers or as a separate unit. This later approach is called an "investigator-initiated multicenter clinical trial" (4). A research grant application for the support of a clinical investigation, whether single-center or multi-center, is reviewed for scientific merit through the regular NIH study section mechanism and competes for funding available through the research grant program.

The Research Contract

Another mechanism for support of a clinical trial is through a contract program initiated by the National Heart, Lung, and Blood Institute. In this case, specific funds are set aside in the Institute's budget to support the investigation. Because support for clinical trials, particularly those concerning preventive regimens, can be expensive, a specialized decision process has been developed by the Institute that has been a useful aid for the formulation, design, conduct, analysis, and dissemination of the results of clinical trials (5). The process includes major decision points at which the Institute commits resources to plan a trial, to conduct a trial, and to terminate the trial. At each decision point, the program is subjected to a series of reviews—peer review, Division advisory group review, Institute review, and Institute Advisory Council review. The reviews center on four basic factors: the state of the science, the feasibility of the proposed trial in terms of the likelihood of the results and the resources required, the potential impact of the trial, and ethical considerations.

Of particular importance to the conduct of a clinical trial is a Data and Safety Monitoring Committee, a committee charged with overseeing the ongoing trial results. The members keep careful watch for signs of toxicity from the intervention as well as a continual analysis of the efficacy of the treatment or preventive regimen. The committee will recommend to the Institute and ultimately the trial's steering committee that the study be terminated if intervention toxicity is noted or if the major question appears to be answered.

Where Do We Stand?

A significant investment of public and private funds has been made for studies of the protease-antiprotease theory of development of pulmonary emphysema. Important contributions to our understanding of the complex pathogenetic mechanisms have been reported. However, many questions remain to be answered before a large-scale clinical trial on treatment of emphysema would be endorsed by the scientific community, the Institute, and its advisors. For example, is there a consensus on the product to be tested? Although the homozygous PiZZ individual is the likely subject, at what point should intervention be considered? Have sufficient PiZZ individuals been identified for participation in a clinical trial or would massive screening programs first have to be undertaken? Will the low number of PiZZ subjects at any given clinical center require participation by such a large number of centers that the financial expense of conducting a trial would be prohibitive?

The NHLBI will continue to encourage and support as many meritorious research grant projects as possible in this important area. Workshops will be held to continue the planning process toward developing a clinical protocol for the testing of products that may be effective in the prevention or management of pulmonary emphysema. In all steps, we will continue to involve the scientific community through the Institute's advisory committees to evaluate the scientific information as it becomes available and to share in the complex decisions that must be made before biomedical resources are committed to initiate a clinical trial to test new agents for treatment of human pulmonary emphysema in a controlled clinical investigation.

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